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Prevalence of central sleep apnea during CPAP titration in people with obstructive sleep apnea syndrome at an altitude of 2640 m

Comment [JM1]: Authors: I have changed the title from patients to people, are you happy with this? Also, the journal does not favour using abbreviations in titles, so please consider writing CPAP in full

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Highlights

- The prevalence of complex sleep apnea (CompSA) at 2640 m above sea level was similar to the prevalence reported in lower altitudes.

- The factors related to CompSA were: being male, having a history of heart failure, and a central apnea index at baseline polysomnogram >5/h.
- These findings may be applicable not only in Bogota but also to populations living at similar altitudes.

ABSTRACT

Background: The occurrence of central apneas when applying positive pressure (CPAP) to patients with obstructive sleep apnea syndrome (OSAS) is called complex sleep apnea (CompSA). This causes poor adherence to CPAP and persistence of symptoms. In Bogota, a city located at an altitude of 2,640 meters above sea level, chronic hypoxemia can generate certain instability of the respiratory system during sleep which could increase the presence of central apneas. The aim was to establish the prevalence of central apneas (central apnea index > 5/h) in adults with moderate or severe OSAS during CPAP titration and the factors associated with this.

Method: Patients over 18 years old with OSAS referred to the Fundacion Neumologica Colombiana Sleep Center, from January 2008 to June 2010. Polysomnogram (PSG) for CPAP titration was performed according to the American Academy of Sleep Medicine criteria. The prevalence was calculated and the clinical and baseline PSG factors associated with the CompSAwere analyzed.

Results: We included 988 patients, 58% men. CompSA prevalence was 11.6%. Factors associated with CompSA were: central apneas in the baseline PSG (OR: 5.34 [3.49-8.16]), history of heart failure (OR: 2.53 [1.58-4.07]) and male sex (OR: 1.68 [1.06-2.69]).

Conclusion: The prevalence of complex sleep apnea in Bogota (11.6%) was intermediate compared to the reported in lower altitudes. The factors associated with the development of CompSA were male sex, heart failure and the presence of central apneas in the baseline PSG.

Keywords:

Central sleep apnea

Complex sleep apnea

Positive airway pressure

Sleep disorder breathing

Altitude

INTRODUCTION

Obstructive sleep apnea-hypopnea syndrome (OSAS) is a common condition in adults. In a study of four cities in Latin America, the general population had a prevalence of symptoms suggestive of OSAS in 4.6% of men and 2.7% of women [1]. In a population-based study in Sao Paulo (Brazil), an apnea-hypopnea index (AHI) <5.0 was present in 61.8% of the participants; an AHI between 5.0 and 14.9 was present in 21.3%, and an AHI higher or equal to 15 was present in 16.9% [2].

Treatment with continuous positive airway pressure (CPAP) is indicated in people with severe OSAS or mild-to-moderate OSAS with associated cardiovascular disease or symptoms [3]. In some individuals, with the application of positive pressure and once the obstructive events are corrected, a pattern of Cheyne-Stokes respiration or central apnea develops and this leads to fragmented sleep. This has been called CPAP-induced central apnea or complex sleep apnea (CompSA) [4], a term that will be used in the present study. It has been proposed that CPAP increases elimination of CO_2, and decreases $PaCO_2$ below the apneic threshold by decreasing airway resistance [5,6], which could cause the occurrence of central apnea. The difficulty in treating people with OSAS and CompSA is that they tend to be less compliant with CPAP and have more daytime sleepiness [7] than those without CompSA.

Bogota is a city located at 2640 m above sea level, which is considered to be at high altitude [8]. It is known that at significant altitudes, chronic hypocapnia and hypoxemia generate certain instabilities of the respiratory system during sleep. This can increase the presence of central apnea and periodic breathing [9], and it has been proposed to be a risk factor for central apnea with positive pressure [10]. The aims of the present study were to establish CompSA prevalence in people with OSA who have been long-term residents in Bogota, Colombia, and to establish which variables in the baseline polysomnogram (PSG) or in the comorbidities are related to its appearance.

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MATERIAL AND METHODS

Participants

The present study included consecutive patients aged over 18, who were long-term residents of Bogota, with moderate-to-severe OSAS (AHI >15/h and had a central apnea index of [CAI] <50% of total AHI). These people were referred for PSG with CPAP titration to the Sleep Center at Fundacion Neumologica Colombiana between January 2008 and June 2010. One hundred and twenty people who received supplemental oxygen during any of the PSG or with split-night studies were excluded. People with recent ascent to the altitude and those with bi-level positive airway pressure titration were also excluded. Medical history, anthropometric data and PSG variables were reviewed. A history of heart failure or atrial fibrillation was recorded in a questionnaire that was completed on the night of the study. With an expected complex sleep apnea prevalence of 6.0% [7], an accuracy of 2%, a Type I error of 1% and a two-tailed hypothesis, a sample size of 936 people was calculated. The Ethics Committee of the Institution approved this study.

Polysomnograms

The PSGs were performed with a digital polysomnograph (Philips Respironics Alice 5 and LE®) using standard PSG montages as follows: EEG signals (C3, C4 and O), right and left oculogram, chin and lower limb electromyogram, nasal pressure cannula (P-TAF), thermistor (Respironics®), thoracic and abdominal effort belts (piezo), finger pulse oxymetry (Masimo®), electrocardiogram (DII), snoring and body position. During the titration PSG performed on a second night, the airflow was derived from CPAP. Manual scoring was performed following the normative of the American Academy of Sleep Medicine (AASM) [11]. Titration was performed according to AASM standards [12] with manual scoring of the study.

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Definitions: *Obstructive apnea*: reduction of airflow greater than 90% in the thermistor, lasting at least 10 s, with respiratory effort. *Central apnea*: reduction of airflow greater than 90%, at least 10 s, without respiratory effort. *Hypopnea*: reduction of the airflow in the nasal cannula greater than 50% for at least 10 s, associated with a decrease of 3% of the oxygen saturation and/or presence of an arousal. The presence of central apnea was considered because the PSG were conducted between 2008 and 2010, and the definition of central hypopnea wasn't established by the AASM until 2012. *CompSA* was defined

as the occurrence of central apnea with an index >5/h during the titration PSG in people with OSAS.

Statistical analysis

The normal distribution of continuous variables was evaluated using a Kolmogorov-Smirnoff test. Qualitative variables were expressed as proportions, and quantitative variables as means and standard deviations, or as medians and interquartile ranges. The Chi-squared statistic was used for comparing categorical variables and the Student's *t*-test or the nonparametric Mann-Whitney U test for continuous variables.

The baseline and titration PSG variables were compared between the groups, with and without CompSA, and in an additional analysis, the variables in the titration PSG between patients with a central apnea index >5/h and those with a central apnea index ≤5/h at baseline polysomnogram. To assess the association between complex apnea with anthropometric and the baseline polysomnogram variables, a logistic regression model was constructed using the variables that showed a *p*-value <0.25 in the univariate analysis. All tests were two-tailed and values <0.05 were considered to be statistically significant. Confidence intervals were calculated at a 95% (90% CI) level. The statistical software SPSS version 15 was used.

RESULTS

Participants

A total of 988 people were included, 58% were males, with a mean age of 58.1 years and a body mass index (BMI) of 31.6. CompSA prevalence was 11.6% (*N* = 115). In the group of CompSA, 73.9% were men and there was no difference in Epworth sleepiness scale in comparison to the group without CompSA.

Polysomnograms

In the diagnostic PSG, the AHI was significantly higher in participants without CompSA ($p<0.001$). Both groups had low sleep efficiency, a low percentage of REM sleep and S3, without significant differences (Table 1). In the titration PSG, the total night AHI ($p<0.001$), the CAI ($p<0.01$), the therapeutic pressure ($p<0.001$) and the oxygen saturation ($p=0.002$) were higher in participants with CompSA (Table 2).

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In the analysis comparing participants with central apnea index >5/h vs those with central apnea index ≤5/h at baseline PSG, those with CAI >5/h had higher AHI (p<0.001) and residual CAI (median 13.0, IQR 7.3 to 24.0) in the titration polysomnogram (p<0.001), without differences in the other PSG variables.

CompSA risk factors

In the group of complex apnea, 29.6% of the participants had a history of heart failure, compared to 15% who had no complex sleep apnea (p<0.001). In the total group, 0.3% had a history of atrial fibrillation, 2.4% stroke and 8.3% were taking sleep induction medications without differences between groups.

Table 3 shows the univariate analysis between clinical parameters and basal PSG data with the occurrence of complex apnea. In the multivariate analysis (Table 4), the factors related to the presence of complex sleep apnea were: CAI >5/h in the baseline PSG (OR 5.34, 95% CI 3.49 to 8.16, p<0.001), a history of heart failure (OR 2.53, 95% CI 1.58 to 4.07, p<0.001), and being male (OR 1.68, 95% CI 1.06 to 2.69, p<0.028).

DISCUSSION

In the present study, a significant number of the participants with OSAS had adapted to the high altitude (2640 m), the complex sleep apnea prevalence was 11.6%, and the factors related to this were: CAI at baseline PSG >5/h, a history of heart failure and being male.

The prevalence of 11.6% is intermediate compared to the prevalence described in lower altitudes of 6.5% to almost 20% [7,13)], and was lower than expected for this altitude above sea level. Pagel et al. [10] analyzed three altitudes above sea level (1421 m, 1808 m, 2165 m), and described, that as altitude increases, central apnea becomes more frequent: 10.6%, 22% and 38.7%, respectively. Probably, the differences in the present results were due to the fact that in Pagel's study, the polysomnograms were split-night, which may have overestimated apnea indices.

In agreement with several authors who claim that the severity of OSAS could be related to CompSA appearance [4,7], the present study found a greater severity of sleep apnea

at baseline PSG in participants with complex sleep apnea. Also, in the titration PSG, the AHI in the whole night was higher in the group of CompSA. This could be explained because these people probably resolve their obstructive events later than those without CompSA. In fact, the average pressure (cmH20) required to abolish obstructive events was higher in these participants. Although statistically significant, the difference of 1 cmH20 is probably of little clinical relevance, and it would not explain why central apnea has been caused by 'overpressure'.

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Regarding risk factors, in the multivariate analysis, the factors related to CompSA were: CAI >5/h in the baseline PSG, a history of heart failure and being male. In the present study, central apneas were more frequent in the baseline PSG of participants with complex sleep apnea, which is similar to the findings of Javaheri [7] and Lehman [14] who reported that 32% and 46% had central apnea This may suggest that these people have an unstable respiratory drive, compared to those who do not develop central apnea with positive pressure. The central apneas were more frequent in non-REM sleep, and were infrequent in REM sleep, as previously reported [7]. Yaegashi et al. found that the CAI in non-REM sleep and supine could be predictors of complex apnea [15].

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A history of heart failure was found to be more common in participants with CompSA. Similarly, Bitter described a high prevalence (18%) in people with heart failure (left ventricular ejection fraction ≤45% and New York Heart Association Class ≥2) [16]. Also, some studies of people without heart failure have described a lower prevalence of CompSA. Westhoff et al. excluded people with high brain natriuretic peptide (BNP) and reported a prevalence of 0.56% [17]. Regarding gender, the present results are similar to some previous reports, finding that CompSA is more frequent in men [4].

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Although some authors have related obesity as a risk factor to CompSA, the literature is divergent [15,18]. In the present study, no differences were found in body mass index between the groups with and without CompSA, nor was there a significant association in the regression model.

The main limitation of the present study was that the CompSA prevalence was likely underestimated because central hypopneas were not scored (due to the fact that this

study was conducted prior to the definition of central hypopnea being established by the AASM). Periodic breathing was not reported, which has been related to respiratory instability at altitude. Although people receiving medications such as opioids and sleep induction medications were not excluded, which could have increased CSA prevalence, only 8% of all participants received this type of drugs: 4.3% in the group with CompSA and 8.8% in the group without CompSA (p=0.065). There were no objective measurements of heart failure with echocardiography or BNP; the diagnosis was based on information from the medical history and patients' medications.

The principal strengths of this work are: that this is the first study of prevalence and risk factors of CompSA in a large population adapted to a high altitude, and that the diagnostic and the titration PSG were made on different nights.

In conclusion, at an altitude of 2640 m, the complex sleep apnea prevalence was 11.6% and the factors related to this were: CAI at baseline PSG >5/h, a history of heart failure and being male. Although the prevalence was not as high as expected, given the high altitude, it is important to recognize and follow-up this disorder. These findings may be relevant not only in Bogota but also in populations living at similar altitudes. Further long-term studies are needed to establish the impact of CompSA on treatment adherence and outcomes.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1. Torre-Bouscoulet L, Vázquez-García JC, Muiño A, Márquez M, López MV, Montes de Oca M, et al. Prevalence of Sleep Related Symptoms in Four Latin American Cities. J Clin Sleep Med 2008; 4(6): 579-85.
2. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive Sleep Apnea Syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Medicine 2010; 11: 441-6.
3. Loube DI, Gay P, Strohl K, Pack A, White D, Collop N. Indications for Positive Airway Pressure Treatment of Adult Obstructive Sleep Apnea Patients: A Consensus Statement. Chest 1999; 115: 863-6.
4. Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. Complex sleep apnea syndrome: is it a unique clinical syndrome? Sleep 2006; 29(9): 1203-9.
5. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. Chest 2007; 131: 595-607.
6. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2004; 169: 623-33.
7. Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. J Clin Sleep Med 2009; 5(3): 205-11.
8. Barry PW, Pollard AJ. Altitude illness. BMJ 2003; 326: 915-9.
9. Kinsman T, Hahn AG, Gore CJ, Wilsmore BR, Martin DT, Chow CM. Respiratory events and periodic breathing in cyclists sleeping at 2,650-m simulated altitude. J Appl Physiol 2002; 92: 2114-8.
10. Pagel JF, Kwiatkowski C, Parnes B. The effects of altitude associated central apnea on the diagnosis and treatment of obstructive sleep apnea: comparative data from three different altitude locations in the Mountain West. J Clin Sleep Med 2011; 7(6): 610-5.
11. Iber C, Ancoli-Israel S, Chesson A, Quan SF, for the American Academy of Sleep Medicine. The AASM Manual for the scoring of sleep and associated

events: Rules, Terminology and Technical Specifications. 1st ed. Westchester, Illinois: American Academy of Sleep Medicine; 2007.

12. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, Iber C, et al. Positive Airway Pressure Titration Task Force of the American Academy of Sleep Medicine. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 2008; 4(2): 157-171.
13. Dernaika T, Tawk M, Nazir S, Younis W, Kinasewitz GT. The significance and outcome of continuous positive airway pressure-related central sleep apnea during split-night sleep studies. Chest 2007; 132: 81-8.
14. Lehman S, Antic N, Thompson C, Catcheside P, Mercer J, McEvoy D. Central sleep apnea on commencement of continuous positive airway pressure in patients with primary diagnosis of obstructive sleep apnea-hyperpnoea. J Clin Sleep Med 2007; 3: 462-6.
15. Yaegashi H, Fujimoto K, Abe H, Ori K, Eda S, Kubo K. Characteristics of Japanese Patients with Complex Sleep Apnea Syndrome: A Retrospective Comparison with Obstructive Sleep Apnea Syndrome. Inter Med 2009; 48: 427-32.
16. Bitter T, Westerheide N, Hossain MS, Lehman R, Prinz C, Kleemeyer A, et al. Complex sleep apnoea in congestive heart failure. Thorax 2011; 66: 402-7.
17. Westhoff M, Arzt M, Litterst P. Prevalence and treatment of central sleep apnoea emerging after initiation of continuous positive airway pressure in patients with obstructive sleep apnoea without evidence of heart failure. Sleep Breath 2012 Mar; 16(1): 71-8.
18. Pusalavidyasagar SS, Olson EJ, Gay PC, Morgenthaler TI. Treatment of complex sleep apnea syndrome: a retrospective comparative review. Sleep Med 2006; 7: 474-9.

Table 1. Characteristics and baseline polysomnographic findings in the groups with and without complex apnea (CompSA).

	Without CompSA (*n*=873)	**CompSA (*n*=115)**	***p*-value**
Age, years	59.0 (50.0 to 67.0)	57.0 (48.0 to 66.0)	0.217
Neck circumference, cm	40.0 (37.0 to 42.2)	41.0 (38.0 to 44.0)	0.028

BMI, kg/cm^2	30.8 (27.7 to 35.0)	29.7 (27.0 to 33.9)	0.154
ESS	10.0 (6.0 to 16.0)	10.0 (6.0 to 15.0)	0.851
AHI, *n*/h	41.8 (27.5 to 62.7)	49.7 (36.0 to 72.9)	0.001
CAI, *n*/h	0.6 (0.1 to 2.5)	5.3 (1.6 to 14.7)	<0.001
OAI, *n*/h	39.1 (25.7 to 59.5)	41.3 (30.4 to 59.6)	0.295
CAI REM, *n*/h	0.0 (0.0 to 0.9)	0.6 (0.0 to 2.3)	<0.001
CAI no-REM, *n*/h	0.6 (0.0 to 2.7)	5.8 (1.7 to 16.2)	<0.001
SE, %	78.0 (65.9 to 86.4)	76.5 (63.3 to 85.7)	0.606
S3, %	13.9 (7.2 to 20.2)	15.1 (7.2 to 22.9)	0.534
REM, %	15.3 (10.6 to 20.0)	15.5 (11.6 to 19.2)	0.965
Mean SpO_2 during events, %	81.0 (77.0 to 85.0)	82.0 (78.0 to 87.0)	0.093

Data are presented as median (IQR)

AHI, apnea hypopnea index; BMI, Body mass index; CAI, central apnea index; ESS, Epworth sleepiness Scale; *n*/h, number of events/hour; OAI, obstructive apnea index; SE, sleep efficiency; SpO_2, Oxygen saturation

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Table 2. Polysomnographic findings of the CPAP titration in participants with and without complex apnea (CompSA).

	Without CompSA (*n*=873)	**CompSA (*n*= 115)**	***p*-value**
SE, %	75.2 (64.4 to 84.3)	72.5 (62.1 to 82.3)	0.157

REM, %	15.7 (10.9 to 20.6)	14.8 (9.2 to 19.0)	0.041
S3, %	19.7 (12.3 to 27.0)	20.3 (12.5 to 27.3)	0.997
Therapeutic pressure, cmH_2O	9.0 (8.0 to 11.0)	10.0 (9.0 to13.0)	<0.001
Mean SpO_2 at therapeutic pressure, %	90.0 (87.0 to 92.0)	91.0 (89.0 to 93.0)	0.002
AHI during whole night, *n*/h	4.9 (2.0 to 9.8)	24.2 (17.1 to 35.7)	<0.001
CAI during whole night, *n*/h	0.4 (0.1 to 1.3)	8.9 (6.9 to 15.7)	<0.001
OAI during whole night, *n*/h	4,1 (1.6 to 8.4)	13,2 (6.9 to 21.2)	<0.001

Data are presented as median (IQR)

CAI, central apnea index; *n*/h, number of events/hour; OAI, obstructive apnea index; SE, sleep efficiency; SpO_2, Oxygen saturation

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Table 3. Demographic characteristics and baseline polysomnographic findings of participants with CompSA (univariate analysis).

Variable	OR	95% CI	*p*-value

Male	2.213	1.430; 3.429	<0.001
Age, years	0.992	0.976; 1.007	0.285
History of heart failure	2.378	1.529; 3.697	<0.001
Neck circumference >40 cm	1.376	0.932; 2.032	0.108
BMI, kg/cm^2	0.987	0.955; 1.021	0.460
ESS	0.996	0.966; 1.027	0.795
SE, %	0.995	0.983; 1.008	0.465
S3, %	1.004	0.985; 1.023	0.683
REM, %	1.003	0.974; 1.032	0.862
CAI >5/h at baseline PSG	5.914	3.926; 8.911	<0.001
Mean SpO_2 during events, %	1.030	1.001; 1.061	0.045

BMI: Body mass index; ESS: Epworth sleep scale; SE: Sleep efficiency; CAI Central Apnea Index; SpO_2: Oxygen saturation

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Table 4. Factors associated with CompSA (multivariate analysis)

Variable	OR	95% CI	*p*-value
CAI > 5/h at the baseline PSG	5.337	3.489; 8.163	<0.0001

History of heart failure	2.534	1.580; 4.067	<0.0001
Male	1.684	1.057; 2.685	0.028

CAI, central apnea index; PSG, polysomnography